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Antimicrobial Activity of Ceftazidime-Avibactam and Comparator Agents Against *Enterobacterales* and *Pseudomonas aeruginosa* With Overexpression of AmpC β-Lactamase From Phase 3 Clinical Trials

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CONCLUSIONS

CAZ-AVI was the most active agent compared with other β-lactams, including carbapenems and aminoglycosides, against AmpC-overproducing *Pseudomonas aeruginosa* with or without coexpression of other β-lactamases (OXAs, PER-1, VEB-9), with a higher proportion of clinical cure than comparators

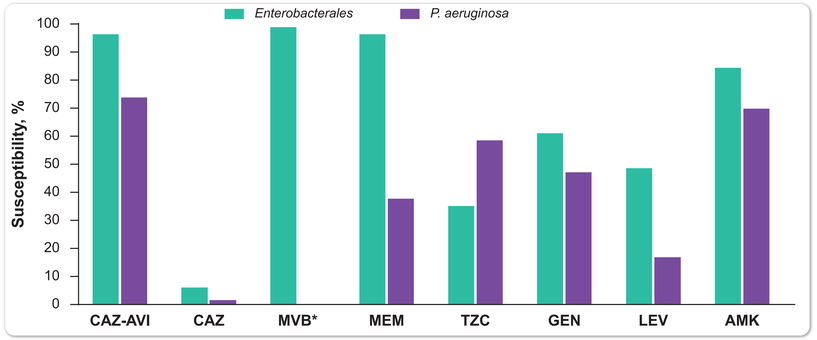
CAZ-AVI was also among the most active agents against AmpC-overproducing *Enterobacterales* with or without coexpression of other β-lactamases (OXA, ESBL, plasmid-encoded AmpC), with >96% isolates susceptible

RESULTS

Susceptibility and Antimicrobial Activity of CAZ-AVI and Comparators Against *Pseudomonas aeruginosa* and *Enterobacterales* (Figures 1–3 and Table 1)

- Against 77 AmpC-overproducing *Enterobacterales* isolates, MVB (98.7% susceptible [S]), CAZ-AVI (96.1% S), and MEM (96.1% S) had similar in vitro activity, with greater in vitro activity than AMK (84.4% S), GEN (61.0% S), LEV (48.1% S), and TZC (35.1% S; **Figure 1**)

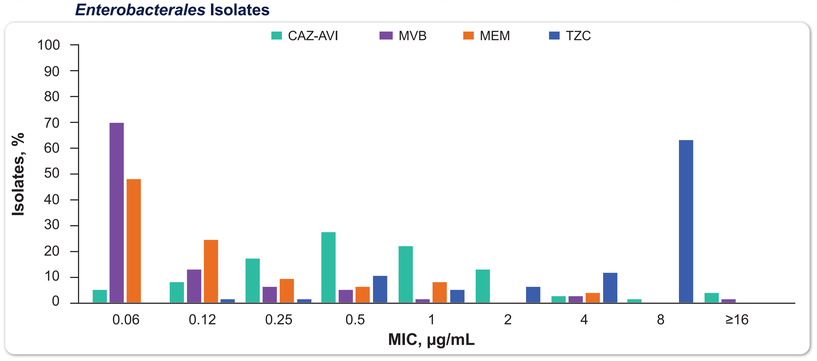
Figure 1. Susceptibility of AmpC-Overproducing *P. aeruginosa* and *Enterobacterales* Isolates to CAZ-AVI and Comparators



AMK, amikacin; CAZ, ceftazidime; CAZ-AVI, ceftazidime-avibactam; GEN, gentamicin; LEV, levofloxacin; MVB, meropenem-vaborbactam, MEM; meropenem; TZC, ceftolozane-tazobactam.
*There are no CLSI breakpoints for MVB against *P. aeruginosa*.

- The MIC distributions against the same *Enterobacterales* isolates were CAZ-AVI (MIC_{50}, 0.5 µg/mL and MIC_{90}, >2 µg/mL), MVB (MIC_{50}, 0.06 µg/mL and MIC_{90}, 0.5 µg/mL), and MEM (MIC_{50}, 0.12 µg/mL and MIC_{90}, 1 µg/mL; **Table 1** and **Figure 2**)

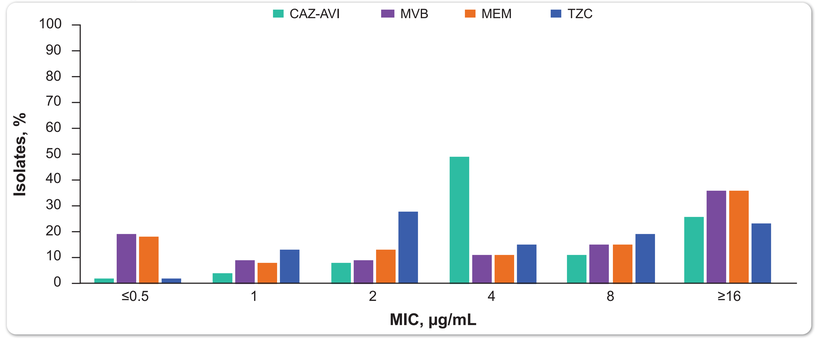
Figure 2. MIC Distribution of CAZ-AVI and Comparators against 77 AmpC Overproducing *Enterobacterales* Isolates



CAZ-AVI, ceftazidime-avibactam; MEM, meropenem; MIC, minimum inhibitory concentration; MVB, meropenem-vaborbactam; TZC, ceftolozane-tazobactam.

- Against 53 AmpC-overproducing *P. aeruginosa* isolates, CAZ-AVI (73.6% S) exhibited greater in vitro susceptibility than AMK (69.8% S), TZC (58.5% S), and MEM (37.7% S; **Figure 1**)
- The MIC distributions against the same *P. aeruginosa* isolates were CAZ-AVI (MIC_{50}, 4 µg/mL and MIC_{90}, >64 µg/mL), MVB (MIC_{50}, 8 µg/mL and MIC_{90}, 32 µg/mL), and MEM (MIC_{50}, 8 µg/mL and MIC_{90}, 32 µg/mL; **Table 1** and **Figure 3**)

Figure 3. MIC Distribution of CAZ-AVI and Comparators Against 53 AmpC Overproducing *P. aeruginosa* Isolates



CAZ-AVI, ceftazidime-avibactam; MEM, meropenem; MIC, minimum inhibitory concentration; MVB, meropenem-vaborbactam; TZC, ceftolozane-tazobactam.

Table 1. Antimicrobial Activity of CAZ-AVI and Comparator Agents Tested Against *P. aeruginosa* and *Enterobacterales*

Pathogen (no. of isolates)	MIC, µg/mL	CAZ-AVI	CAZ	MVB	MEM	TZC	GEN	LEV	AMK
Pseudomonas aeruginosa (n=53)	MIC_{50}	4	64	8	8	4	8	>16	8
	MIC_{90}	>64	>64	32	32	>64	>32	>16	128
	MIC range	0.06–>64	0.06–>64	0.06–>64	0.06–>64	0.06–>64	0.5–>32	0.25–>16	1–>128
Enterobacterales (*Citrobacter freundii* complex, *Klebsiella aerogenes*, *Enterobacter cloacae*, *Escherichia coli*, *Serratia marcescens*; n=77)	MIC_{50}	0.5	64	0.06	0.12	8	1	2	2
	MIC_{90}	2	>64	0.5	1	>64	>32	>16	>128
	MIC range	0.25–>64	0.5–>64	0.03–>64	0.03–>64	0.12–>64	0.25–>32	0.06–>16	0.5–>16

AMK, amikacin; CAZ, ceftazidime; CAZ-AVI, ceftazidime-avibactam; GEN, gentamicin; LEV, levofloxacin; MIC, minimum inhibitory concentration; MVB, meropenem-vaborbactam, MEM; meropenem; TZC, ceftolozane-tazobactam.MEM; meropenem; TZC, ceftolozane-tazobactam.

Molecular Characterization of AmpC-Overexpressing Isolates and Coexpression of Other β-Lactamases (Table 2)

- The majority of AmpC-overexpressing *Enterobacterales* isolates had coexpression with other β-lactamases, including combinations with ESBL (CTX-M, TEM, SHV), OXA, and plasmid-encoded AmpC (DHA, CMY)
- Among isolates with β-lactamase coexpression, 98% (40/41) were susceptible to CAZ-AVI
- Most chromosomal AmpC-overexpressing *P. aeruginosa* isolates with coexpression of other β-lactamases, including several OXA variants and ESBL (PER-1), were susceptible to CAZ-AVI (71% [10/14])

Table 2. Molecular Characterization of AmpC-Overexpressing Isolates and Coexpression of Other β-Lactamases

	Organism	AmpC Overexpression and Other β-Lactamases	Number
Enterobacterales	*Citrobacter freundii* complex	Chrom. AmpC overexpression	6
		Chrom. AmpC overexpression + CTX-M-15-like + OXA-1/30 + TEM-1 or + DHA-4	4
		Chrom. AmpC overexpression + CTX-M-3-like or + TEM-1	2
		Chrom. AmpC overexpression + CTX-M-15-like + CTX-M-3-like + OXA-1/30 + TEM-1	2
	Klebsiella aerogenes	Chrom. AmpC overexpression	8
	Enterobacter cloacae	Chrom. AmpC overexpression + CTX-M-15-like or + CTX-M-3 + OXA-1/30 or + TEM-1	19
		Chrom. AmpC overexpression	17
		Chrom. AmpC overexpression + TEM-1 or + SHV-12 or PER-1	5
		Chrom. AmpC overexpression + CTX-M-3-like + TEM-1 or + SHV-12	4
		Chrom. AmpC overexpression + OXA-1/30 or + SHV-12 + TEM-1	3
		Chrom. AmpC overexpression + CTX-M-15-like + NDM-1 + TEM-1	1
	Escherichia coli	Chrom. AmpC overexpression	4
		Chrom. AmpC overexpression + CMY-42	1
	Serratia marcescens	Chrom. AmpC overexpression	1
Pseudomonas aeruginosa		Chrom. AmpC overexpression	39
		Chrom. AmpC overexpression + OXA-2, or OXA-14, or OXA-17, + PER-1	12
		Chrom. AmpC overexpression + OXA-10 or + VEB-9	2

Chrom, Chromosome.

Clinical Cure at TOC in Patients with Baseline AmpC-overproducing *Enterobacterales* or *Pseudomonas*

- Clinical cures at TOC in patients with baseline AmpC-overproducing *Enterobacterales* were 81% (21/26) in CAZ-AVI group vs 85% (17/20) in comparator group
- Clinical cures at TOC in patients with baseline AmpC-overproducing *P. aeruginosa* were 86% (12/14) in CAZ-AVI group vs 75% (9/12) in comparator group

INTRODUCTION

- AmpC overproduction is a main mechanism of carbapenem resistance in the absence of acquired carbapenemases
- Gram-negative pathogens harboring a chromosomal drug-inducible AmpC have become a major cause of resistance to widely used third- and fourth-generation cephalosporins when AmpC β-lactamases are overproduced[1,2]
- Ceftazidime-avibactam (CAZ-AVI) has demonstrated potent in vitro activity and clinical efficacy against AmpC-producing *Pseudomonas aeruginosa* and *Enterobacterales* that are resistant to carbapenems and other β-lactams
- This study evaluated the in vitro activity of CAZ-AVI and clinical response against AmpC-overexpressing *P. aeruginosa* and *Enterobacterales* collected from 4 clinical trials

METHODS

Bacterial isolates

- Nonduplicate clinical isolates of AmpC-overproducing *Enterobacterales* (n=77) and *P. aeruginosa* (n=53) were collected from 4 CAZ-AVI clinical trials: RECLAIM (complicated intra-abdominal infection [cIAI], NCT01499290/NCT01726023), REPRISE (cIAI/complicated urinary tract infection [cUTI], NCT01644643), RECAPTURE (cUTI, NCT01595438/NCT01599806), and REPROVE (hospital-acquired/ventilator-associated pneumonia, NCT01808092)
- The *Enterobacterales* included *Enterobacter cloacae* (n=49), *Citrobacter freundii* complex (n=14), *Klebsiella aerogenes* (n=8), *Escherichia coli* (n=5), and *Serratia marcescens* (n=1)

Resistant subsets

- Quantitative PCR and microarray data (Check-Points Health B.V., Wageningen, Netherlands) were used to characterize presence and expression level of AmpC and coharbored β-lactamases including extended spectrum β-lactamase (ESBL; CTX-M, TEM, SHV), AmpC (DHA, CMY), OXA, NDM, and VEB

Susceptibility testing

- In vitro susceptibility testing was performed by broth microdilution method using a custom-made panel (ThermoFisher Scientific, Waltham, MA) consisting of CAZ-AVI, ceftazidime (CAZ), meropenem (MEM), meropenem-vaborbactam (MVB), ceftolozane-tazobactam (TZC), gentamicin (GEN), levofloxacin (LEV), and amikacin (AMK)
- Clinical and Laboratory Standards Institute (CLSI) test methods were followed, and CLSI breakpoints were applied for susceptibility interpretations

Clinical outcome evaluation

- Clinical response at test of cure (TOC) was assessed in patients with baseline AmpC-overproducing *Enterobacterales* and baseline AmpC-overproducing *P. aeruginosa* treated with CAZ-AVI or comparators
- TOC was assessed at 21–25 days after randomization (REPRISE, RECAPTURE, and REPROVE), or at 28–35 days after randomization (RECLAIM)

DISCLOSURES

This study was supported by Allergan (Dublin, Ireland; prior to its acquisition by AbbVie). Allergan (now AbbVie) was involved in the design and decision to present these results. Lynn-Yao Lin, Dmitri Debabov, and William Chang are employees of AbbVie. Urania Rappo was an employee of Allergan plc, prior to its acquisition by AbbVie, at the time of study conduct and analysis and is currently an employee of BiomX, Inc.

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